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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,803	05/22/2001	Jeffrey J. Rade	71699/55591	8907

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,803	RADE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,33-49 and 52-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,33-49 and 52-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 21, 2006 has been entered.

The response and amendment filed May 30, 2006 have been entered. Claims 70, and 71 have been amended. Claims 29, 30, 33-49, 52-72 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejection will not be reiterated.

Claim Objections

Applicant is advised that should claim 29 be found allowable, claim 59 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing

one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 30, 33-49, 52, 59, 60, 61, 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Newby et al* (Curr Opin Cardiol 1999;14:489-94), in view of *Waugh et al* (Circ Res 1999;84:84-92, IDS) and *Soares et al* (J Immunol 1998;161:4572-82).

The claims are directed to a method for treating a mammal to resist early vein graft failure by introducing into autologous endothelial cells of a vein graft an effective amount of a nucleic acid encoding a thrombomodulin (TM), and further encodes a NF-κB inhibitor. The specification teaches that early graft failure is typically due to occlusive *thrombosis* (Specification, page 1, last paragraph and claim 37), and thus inhibiting thrombosis would make a mammal resist early vein graft failure.

Newby et al teach targeted gene therapy in humans for preventing vein graft failure, particularly preventing early thrombosis, wherein the method comprises introducing into autologous vein graft a nucleic acid encoding thrombomodulin (e.g. column 2, page 491). *Newby et al* teach that adenovirus expressing thrombomodulin

has proven effective in inhibiting thrombosis in a vascular stasis/injury model citing the report from *Waugh et al. Newby et al* go on to teach although the approach has yet to be applied to vein grafts, "BUT THE RATIONALE FOR THIS APPLICATION IS STRONG".

Waugh et al supplemented *Newby et al* by illustrating the effect of expressing exogenous TM on inhibiting thrombosis in a vascular graft *in vivo*. *Waugh et al* constructed an adenoviral vector encoding the TM operably linked to a Rous sarcoma virus ITR promoter, and delivered such locally to exposed common femoral artery. *Waugh et al* teach because it is impossible to precisely evaluate local TM levels *in vivo*, they monitored the formation of vascular thrombus *in vivo* as a functional assay for expression of TM. Vascular samples were collected six days after the adenoviral vector delivery and three days after initiation of the thrombosis, which clearly showed that local over-expression of TM via the Adv-TM nucleic acids was sufficient for preventing and treating *in vivo* arterial thrombus formation (page 88, and fig.5), which indirectly evidenced that the protein C activation has lasted at least one or two days. *Waugh et al* also measures APC to show the correlation between activation of protein C and TM overexpression in endothelial cells *in vitro*. Figure 3 shows that Adv/RSV-TM construct was able to produce APC at a level 153% of controls.

Although the experiment of *Waugh et al* was not conducted on a vein graft, there is no apparent reason why the Adv-TM would not suppress a thrombosis process that occurred in a vein graft, particularly considering that TM is routinely produced by endothelial cells, which cover the inner surface of a vessel regardless the vessel is an artery, a vein, or an artificial graft.

As to the limitation that the nucleic acid encoding a TM would further encodes a NF-κB inhibitor, *Newby et al* in view of *Waugh et al* do not teach suppressing vascular thrombosis with a NF-κB inhibitor. As an initial matter, it is noted since *Newby et al*, in view of *Waugh et al* renders instant claims obvious, one skilled intending to practice the invention would have a reasonable expectation of success using Adv-TM even if it further encodes a placebo.

Moreover, *Soares et al* supplemented *Newby et al* in view of *Waugh et al* by establishing that it was well known in the art that a NF-κB inhibitor can enhance graft survival by blocking proinflammatory gene associated with endothelial cell activation, and by illustrating that a NF-κB inhibitor indeed enhances graft survival. *Soares et al* teach transducing human vascular endothelial cells with a NF-κB inhibitor (Adenovirus-mediated expression of a dominant negative mutant of p65/RelA, p65RHD) to suppress the inflammatory response mediated by the NF-κB (e.g. fig. 7), and go on to teach p65RHD is a candidate gene for preventing xenograft rejection (e.g. last paragraph, page 4581).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method as taught by *Newby et al* in view of *Waugh et al* by further including a NF-κB inhibitor as taught by *Soares et al* in the Adv-TM construct for resisting early vein graft failure with a reasonable expectation of success. The skilled in the art would have been motivated to combine the two because both target genes achieve a common goal of extending graft survival. The skilled in the art would have had a reasonable expectation of success when combining the two

effective agents, given the results obtained in the two separate experiments, and thus the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 53-55, and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Newby et al* (Curr Opin Cardiol 1999;14:489-94), in view of *Waugh et al* (Circ Res 1999;84:84-92, IDS) and *Soares et al* (J Immunol 1998;161:4572-82) as applied to claims 29, 30, 33-49, 52, 59, 60, 61, 68-69 above, and further in view of *Hardy et al* (J Virol 1997;71:1842-9).

The combined teachings of *Newby et al* in view of *Waugh et al* and *Soares et al* do not discuss the specifics of the adenoviral vector, but such has been taught by *Hardy et al* and well known in the art. *Hardy et al* teach constructing an adenoviral vector comprising two ITRs and CMV promoter (e.g. fig. 1), and using such for cloning and expressing a therapeutic gene of interest.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the adenoviral vector as taught by *Hardy et al* in the method as taught by *Newby et al* in view of *Waugh et al* and *Soares et al* with a reasonable expectation of success. Given the numerous expression vectors known in the art, these limitations fall within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 56-58, and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Newby et al* (Curr Opin Cardiol 1999;14:489-94), in view of *Waugh et al* (Circ Res 1999;84:84-92, IDS) and *Soares et al* (J Immunol 1998;161:4572-82) as applied to claims 29, 30, 33-49, 52, 59, 60, 61, 68-69 above, and further in view of *Qing et al* (J Virol 1997;71:5663-7).

The combined teachings of *Newby et al* in view of *Waugh et al* and *Soares et al* do not teach the specifics of a AAV vector, but such has been taught by *Qing et al* and well known in the art. *Qing et al* teach constructing an AAV vector comprising a RSV ITR promoter and using such for expressing a therapeutic gene (e.g. figure 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the AAV vector as taught by *Qing et al* in the method as taught by *Newby et al* in view of *Waugh et al* and *Soares et al* with a reasonable expectation of success. Given the numerous expression vectors known in the art, these limitations fall within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Vassalli et al* (Cardiovasc Res 1997;35:459-69), in view of *Soares et al* (J Immunol 1998;161:4572-82).

Claim 70 is directed to a method for treating a mammal to resist early vascular or vein graft failure by contacting endothelial cells with an artificial graft, wherein the

endothelial cells are transduced with an effective amount of a nucleic acid encoding a thrombomodulin (TM), wherein the nucleic acid further encodes a NF-kB inhibitor. The specification teaches that early graft failure is typically due to occlusive *thrombosis* (Specification, page 1, last paragraph and claim 37), and thus inhibiting thrombosis would make a mammal resist early vein graft failure.

Claim 71 is directed to a method of making an artificial vascular graft. Claim 72 is directed to the artificial graft made by claim 71.

Vassalli et al teach that conventional antithrombotic treatment is not uniformly successful and is associated with hemorrhagic side effects. Gene therapy could be a potential alternative because its unique ability to express an antithrombotic gene at selected sites of the vessel walls either directly *in vivo* or *ex vivo* prior to cell transplant (e.g. abstract). *Vassalli et al* teach this approach may particularly useful for enhancing patency of prosthetic vascular grafts because they are smaller in diameter compared to autologous arteries and veins (§ 2.7). *Vassalli et al* teach seeding (contacting) an artificial vascular graft with endothelial cells transduced with a nucleic acid encoding an antithrombotic gene t-PA, and reduced thrombus formation (column 2, page 462). *Vassalli et al* go on to teach that thrombomodulin is one of the candidate gene of choice for such gene therapy strategy (table 1). *Vassalli et al* also pointed to the success of decreased thrombus formation using adenoviral vector expressing TM in human endothelial cells *in vitro* (paragraph bridging pages 464-5). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transduce endothelial cells with either or both nucleic acids encoding the t-PA or TM as

suggested by *Vassalli et al* and seeding such on an artificial graft with a reasonable expectation of success.

As to the limitation that the nucleic acid encoding a TM would further encodes a NF-κB inhibitor, *Vassalli et al* do not teach suppressing vascular thrombosis with a NF-κB inhibitor. As an initial matter, it is noted since the teaching of *Vassalli et al* renders instant claims obvious, one skilled intending to practice the invention would have a reasonable expectation of success using Adv-TM alone even if it further encodes a placebo.

Moreover, *Soares et al* supplemented *Vassalli et al* by establishing that it was well known in the art that a NF-κB inhibitor can enhance graft survival by blocking proinflammatory gene associated with endothelial cell activation, and by illustrating that a NF-κB inhibitor indeed enhances graft survival. *Soares et al* teach transducing human vascular endothelial cells with a NF-κB inhibitor (Adenovirus-mediated expression of a dominant negative mutant of p65/RelA, p65RHD) to suppress the inflammatory response mediated by the NF-κB (e.g. fig. 7), and go on to teach p65RHD is a candidate gene for preventing xenograft rejection (e.g. last paragraph, page 4581).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method as taught by *Vassalli et al* by further including a NF-κB inhibitor as taught by *Soares et al* in the nucleic acid construct for resisting early vascular or vein graft failure with a reasonable expectation of success. The skilled in the art would have been motivated to combine the two because both target genes achieve a common goal of extending graft survival. The skilled in the art

would have had a reasonable expectation of success when combining the two effective agents, given the results obtained in the two separate experiments, and thus the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 30, 33-49, 52-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a mammal to resist early vein graft failure by introducing into endothelial cells of an autologous graft a nucleic acid encoding thrombomodulin and/or a NF-kB inhibitor, does not reasonably provide enablement for doing so by introducing into endothelial cells of an autologous graft a nucleic acid encoding EPCR. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the

art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to a method for treating a mammal to resist early vein graft failure by introducing into endothelial cells of an autologous graft at least one of the following nucleic acids encoding thrombomodulin and/or a NF-κB inhibitor, and endothelial cell protein C receptor (EPCR). The specification teaches the role of EPCR in vascular thrombosis, and contemplates by over-expressing EPCR, one can reduce early vascular graft failure. The specification does not reduce to practice showing the theory would actually work.

In a post-filing publication of the applicant (*Kim et al*, Circ Res 2002;90:205-12), the authors examined both the role of TM and EPCR in vein graft failure, and concluded that the thrombomodulin but not EPCR is dramatically reduced early after vein graft, (1st paragraph, page 210), which impairs vein graft thromboresistance (e.g. title and abstract). As such, supplementing EPCR does not appear to be enabled for resist vein graft failure, since there is no shortage of the EPCR in vein graft. In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the reference.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation commensurate with the scope of the claims.

Conclusion

No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Victor Barlow**, whose telephone number is (571) 272-0506. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

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QJL
June 9, 2006